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Prognostic role of adjuvant radiotherapy in triple-negative breast cancer: A historical cohort study

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The value of adjuvant radiotherapy in triple-negative breast cancer (TNBC) is currently debated. We assessed the association between adjuvant radiotherapy and survival in a large cohort of Asian women with TNBC. Women diagnosed with TNBC from 2006 to 2011 in five Asian centers ($N = 1,138$) were included. Survival between patients receiving mastectomy only, breast-conserving therapy (BCT, lumpectomy and adjuvant radiotherapy) and mastectomy with radiotherapy were compared, and adjusted for demography, tumor characteristics and chemotherapy types. Median age at diagnosis was 53 years (range: 23–96 years). Median tumor size at diagnosis was 2.5 cm and most patients had lymph node-negative disease. The majority of patients received adjuvant chemotherapy ($n = 861$, 76%) comprising predominantly anthracycline-based regimes. In 775 women with T1-2, N0-1, M0 TNBCs, 5-year relative survival ratio (RSR) was highest in patients undergoing mastectomy only (94.7%, 95% CI: 88.8–98.8%), followed by BCT (90.8%, 95% CI: 85.0–94.7%), and mastectomy with radiotherapy (82.3%, 95% CI: 73.4–88.1%). The adjusted risks of mortality between the three groups were not significantly different. In 363 patients with T3-4, N2-3, M0 TNBCs, BCT was associated with highest 5-year RSR (94.1%, 95% CI: 81.3–99.4%), followed by mastectomy with radiotherapy (62.7%, 95% CI: 54.3–70.1%), and mastectomy only (58.6%, 95% CI: 43.5–71.6%). Following multivariable adjustment, BCT and mastectomy with radiotherapy remained significantly associated with lower mortality risk compared to mastectomy only. Overall, adjuvant radiotherapy was associated with higher survival in women aged <40 years, but not in older women. Adjuvant radiotherapy appears to be independently associated with a survival gain in locally advanced as well as in very young TNBC.

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Key words: triple-negative breast cancer, adjuvant radiotherapy, postmastectomy, survival, Asia

Abbreviations: BCT: breast-conserving therapy; CI: confidence interval; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; HR: hazard ratio; NCCS: National Cancer Centre; NUH: National University Hospital; PR: progesterone receptor; QMTWH: The University of Hong Kong, Queen Mary and Tung Wah Hospital; RSR: relative survival ratio; TNBC: triple-negative breast cancers; TTSH: Tan Tock Seng Hospital; UMMC: University Malaya Medical Centre

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What's new?
In Asia, the burden of triple negative breast cancer (TNBC) is substantial, in part due to the younger age at breast cancer diagnosis in the population. The value of adjuvant radiotherapy in TNBC, and whether it should become a standard option following mastectomy, is under debate. In a large unselected prospective cohort of Asian patients, this study shows that, irrespective of type of surgery and chemotherapy, adjuvant radiotherapy is associated with a significant survival gain in locally advanced TNBC, but not in early stages. Adjuvant radiotherapy may also be particularly beneficial in women under 40 but not in older women.

Triple-negative breast cancers (TNBC), which accounts for 12–17% of all breast cancers,[1] are associated with a higher risk of early development of visceral metastasis and local recurrence compared to other breast cancer subtypes.[2] They continue to pose a challenge in clinical practice given the lack of treatment options. While chemotherapy remains the mainstay of treatment, there is currently a gap in knowledge on the importance and role of adjuvant radiotherapy in TNBC.[3]

Results from studies investigating the prognostic role of adjuvant radiotherapy in TNBC have been far from conclusive.[4–9] A large retrospective cohort study found that in patients with T1-2,N0 TNBC, adjuvant radiotherapy following breast-conserving surgery was associated with superior recurrence-free survival compared to mastectomy alone,[4] While the apparent gain in recurrence-free survival conferred by adjuvant radiotherapy in our study was not translated into an overall survival benefit, a large multicenter randomized trial from China demonstrated that postmastectomy radiotherapy in women with Stage I–II TNBC was associated with a significant 13.7% absolute reduction in locoregional relapse and 11.7% improvement in overall survival.[5] However, other studies did not find an association.[6–9] It is noticeable that the population included in the clinical trial in China differed from previously reported series from the West, with two-thirds of patients being young and/or having T2 stages or higher.[5]

In Asia, the burden of TNBC is substantial, in part owing to the younger age at diagnosis of breast cancer in the population.[10–12] In a recent single institutional study from Malaysia, TNBCs comprised almost one-third of all newly diagnosed cases, and the age-standardized incidence was higher in certain ethnic groups such as in Malays and the indigenous populations.[13] Furthermore, Asian breast cancer patients have a preponderance to opt for mastectomy, even when presenting with small tumors.[14–16] Hence, if radiotherapy truly confers a survival benefit in TNBC, the question of whether adjuvant radiotherapy should be discussed as a standard option following mastectomy is pertinent.[3]

Within a large multiethnic cohort of Asian TNBC patients, we determined the association between adjuvant radiotherapy and survival following the diagnosis of breast cancer.

Methods

Setting

Data for the current study were obtained from the hospital-based breast cancer registries in five Asian centers, *i.e.*, University Malaya Medical Centre (UMMC), Malaysia, National Cancer Centre (NCCS), Singapore, National University Hospital (NUH), Singapore, Tan Tock Seng Hospital (TTSH), Singapore and The University of Hong Kong, Queen Mary and Tung Wah Hospital (QMTWH), Hong Kong. All five are tertiary referral centers with prospective breast cancer registration.[10,17]

Our study obtained ethics approval from the University Malaya Medical Centre's Ethics Committee, the National Healthcare Group (NHG) Domain Specific Review Board (DSRB), the SingHealth Centralised Institutional Review Board (CIRB) and Institutional Review Board of the University of Hong Kong. As the study relies on nonidentifiable registry-based data, the need to obtain informed consent was waived.

In our study, staging for breast cancer was based on AJCC Cancer Staging Manual Seventh Edition. All the hospitals in our study subscribe to internationally recognized external quality assessment scheme for immunocytochemistry (Supporting Information Table 1). The estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status were determined by immunoperoxidase staining. As our study included patients diagnosed before implementation of the 2010 American Society of Clinical Oncology/College of American Pathologists guideline recommendations for IHC testing of ER/PR,[18] expression of ER and PR was considered negative if staining of the tumor cell nuclei was <10%. The DAKO classification system was used to interpret HER2 expression, based on a staining intensity that was classified as 0 (negative), 1+, 2+ or 3+. Only a report of negative or 1+ was taken as HER2 negative. Tumors with equivocal HER2 status (score 2+) were further subjected to fluorescence *in situ* hybridization (FISH) to confirm lack of HER2 gene amplification. Patients with equivocal HER2 status whom did not undergo FISH were excluded.

Study participants

In our study, we only considered 1,576 patients newly diagnosed with TNBC between 2006 and 2011, as routine testing of breast cancers for HER2 status was done in most of the hospitals after 2005. Following exclusion of TNBC patients with Stage IV disease ($n = 126$), those who had breast-conserving surgery without adjuvant radiotherapy ($n = 136$) and women with unknown adjuvant chemotherapy or radiotherapy status ($n = 176$), we had included 1,138 women for analysis: 375 patients from UMMC, 111 patients from NUH, 369 patients from NCCS, 155 from TTSH and 128 patients from QMTWH.

Adjuvant chemotherapy

In all the participating centers, patients with TNBC were not treated differently compared to patients with other breast cancer subtypes. The large majority of patients received anthracyclines ± taxane-based chemotherapy.

Locoregional management

Patients treated with breast-conserving surgery received adjuvant chemotherapy followed by whole breast radiotherapy. In UMMC, patients received 40 Gy in 15 daily fractions, for 5 days a week for a period of 3 weeks, using megavoltage photons, conventional or three-dimensional (3D) planned with two tangential beams, followed by a boost to the tumor bed of 16 Gy in eight fractions, over 1.5 weeks, using electrons. Ipsilateral supraclavicular fossa was only irradiated in patients with four or more lymph nodes involved, using direct anterior megavoltage photon, whereas in those with one to three nodes, ISF radiation was optional.

In NCCS, TTSH, NUH[19] and QMTWH, patients received 50 Gy in 25 fractions to the whole breast. Treatment was administered 5 days a week for a duration of 5 weeks followed by a 10 Gy boost to the tumor bed (five fractions, daily over 1 week). All patients were treated with megavoltage photons. Patients were mostly planned using 3D conformal radiotherapy except for some patients treated in NCCS before 2007 who were conventionally planned. The ipsilateral supraclavicular fossa was treated if patients had node-positive disease.

Modified radical mastectomy was the most common type of mastectomy and was accompanied by at least a level II axillary dissection. In all centers, postmastectomy radiotherapy was indicated for patients presenting with four or more positive axillary lymph nodes, those with tumors measuring 5 cm or morein size, women with T4 disease and patients with positive surgical margins. Administration of postmastectomy radiotherapy was discussed with patients with one to three nodes.

In UMMC, postmastectomy radiotherapy was delivered at 40 Gy in 15 daily fractions, for 5 days a week for a period of 3 weeks. Criteria for ISF radiation were similar to BCT.

In NUH, NCCS, TTSH and QMTWH, radiation was given to the chest wall and supraclavicular fossa (if nodes-positive disease) using mega-voltage X-rays, delivering 50 Gy in 25 fractions over 5 days a week, for a period of 5 weeks.

Patient follow-up

In UMMC, NUH and QMTWH, mortality data of all patients were obtained through direct linkage with the respective National Registration Departments. Dates of censoring were March 31, 2013 in UMMC, July 31, 2013 in NUH and March 31, 2013 in QMTWH. In NCCS and TTSH, where active follow-up was undertaken, dates of death were obtained either based on hospital records or through patients' next of kin. In these two centers, date of censoring was based on patients' last contact in the specialist breast cancer clinics, hospital laboratories or imaging facilities. Data on disease recurrence were not available to a large extent in most centers. Follow-up was calculated from date of diagnosis of breast cancer to the date of death or end of follow-up.

Study variables

Outcome of the study was all-cause mortality. Determinants of mortality included type of locoregional treatment (BCT, mastectomy only, mastectomy with radiotherapy) and demographic characteristics (hospital, age at diagnosis, self-declared ethnicity including Malay, Chinese, Indian or other races). Tumor characteristics included histologically determined tumor size (in cm), number of positive axillary lymph nodes, tumor grade (Scarff–Bloom–Richardson classification Grade 1, Grade 2 or Grade 3) and lymphovascular invasion (present, absent). In women subjected to neoadjuvant chemotherapy, we included the tumor size and lymph nodes measured before neoadjuvant chemotherapy administration. Treatment data included surgical margin status (positive, negative), neoadjuvant chemotherapy (yes, no) and adjuvant chemotherapy administration (yes, no). Type of adjuvant chemotherapy was broadly classified into three categories, *i.e.*, first generation, second generation (antracycline based) and third generation (taxane-based) (http://www.adjuvantonline.com/breasthelp0306/Generations.html).

Statistical analysis

Categorical variables were described by proportions and compared using χ^2 test. Continuous variables were expressed in medians and compared using Kruskal–Wallis test. Demographic, tumor and treatment characteristics were compared between those receiving breast-conserving therapy, mastectomy only and mastectomy with radiotherapy. Within patients subjected to mastectomy, we performed a multivariable logistic regression analysis to identify factors, which were independently associated with postmastectomy radiotherapy administration.

To approximate disease-specific survival, we computed relative survival, which is a widely used measure of cancer survival given that it does not rely on accurate cause of death coding.[20,21] Relative survival is the ratio of overall survival observed in TNBC patients to the survival that would have been expected had they been subjected only to the mortality rates of the general female population (background mortality) matched for age, calendar year and country of residency. Expected survival was derived from the respective life tables for the general population in Malaysia, Singapore and Hong Kong.

Given that locoregional management is administered largely based on disease staging (*i.e.*, tumor size, lymph node

Table 1. Demographic, tumor and treatment characteristics in 1,138 Asian women with nonmetastatic triple-negative breast cancer

	Overall ($N = 1,138$)	Breast-conserving therapy ($n = 366$)	Mastectomy only ($n = 354$)	Mastectomy and radiotherapy ($n = 418$)	*p* Values	Adjusted odds ratio for postmastectomy radiotherapy[1]
Center, *n* (%)						
UMMC	375 (33.0)	75 (20.5)	137 (39.0)	163 (39.0)		1.00
NUH	111 (9.8)	49 (13.4)	37 (10.5)	25 (13.4)		0.66 (0.14–3.22)
NCCS	369 (32.4)	146 (39.9)	75 (21.2)	148 (35.4)	<0.001	2.27 (1.43–3.62)[2]
QMTWH	128 (11.2)	35 (9.6)	54 (15.3)	39 (9.3)		0.99 (0.55–1.80)
TTSH	155 (13.6)	61 (16.7)	51 (14.4)	43 (10.3)		0.81 (0.39–1.65)
Age at diagnosis, median in years	53	49	59	53	<0.001	0.98 (0.96–0.99)[2]
Ethnicity, *n* (%)						
Chinese	824 (72.5)	252 (68.9)	276 (78.2)	296 (71.0)		1.00
Malay	144 (12.7)	50 (13.7)	28 (7.9)	66 (15.8)	0.02	1.46 (0.80–2.68)
Indian	100 (8.8)	36 (9.8)	29 (8.2)	35 (8.4)		1.01 (0.54–1.92)
Other races	68 (6.0)	28 (7.7)	20 (5.7)	20 (4.8)		0.52 (0.23–1.19)
TNM tumor stage, *n* (%)					<0.001	1.19 (1.08–1.31)[2,3]
T1	389 (34.2)	176 (48.1)	137 (38.7)	76 (18.2)		
T2	501 (44.0)	143 (39.1)	163 (46.1)	195 (46.7)		
T3	128 (11.2)	22 (6.0)	27 (7.6)	79 (18.9)		
T4	120 (10.6)	25 (6.8)	27 (7.6)	68 (16.2)		
TNM nodal stage, *n* (%)					<0.001	1.10 (1.05–1.14)[2,3]
N0	631 (55.4)	260 (71.0)	268 (75.7)	103 (24.6)		
N1	333 (29.3)	78 (21.3)	63 (17.8)	192 (45.9)		
N2	92 (8.1)	19 (5.2)	11 (3.1)	62 (14.9)		
N3	82 (7.2)	9 (2.5)	12 (3.4)	61 (14.6)		
Tumor grade, *n* (%)						
Grade 1	21 (2.0)	6 (1.8)	12 (3.8)	3 (0.8)		0.41 (0.08–2.11)
Grade 2	205 (19.7)	59 (17.5)	75 (23.7)	71 (18.3)	0.008	1.08 (0.68–1.72)
Grade 3	815 (78.3)	272 (80.7)	229 (72.5)	314 (80.9)		1.00
Unknown	97	29	38	30		
Lymphovascular invasion, *n* (%)						
Present	323 (34.1)	69 (24.0)	85 (28.8)	169 (46.4)	<0.001	1.53 (0.98–2.39)
Absent	623 (65.9)	218 (76.0)	210 (71.2)	195 (53.6)		1.00
Unknown	192	79	59	54		
Neoadjuvant chemotherapy, *n* (%)						
Yes	144 (13.0)	37 (10.4)	23 (6.8)	84 (20.4)	<0.001	3.88 (2.09–7.19)[2]
No	964 (87.0)	320 (89.6)	317 (93.2)	327 (79.6)		1.00
Unknown	30	9	14	7		
Surgical margin status, *n* (%)						
Free	683 (87.3)	213 (91.0)	203 (89.4)	267(83.2)	0.01	1.00
Involved	99 (12.7)	21 (9.0)	24 (10.6)	54 (16.8)		2.07 (1.17–3.66)[2]
Unknown	356	132	127	97		
Chemotherapy, *n* (%)						
No	275 (24.2)	71 (19.4)	145 (41.2)	59 (14.1)		1.00
Yes	861 (75.8)	295 (80.6)	207 (58.8)	359 (85.9)	<0.001	

Table 1. Demographic, tumor and treatment characteristics in 1,138 Asian women with nonmetastatic triple-negative breast cancer (Continued)

	Overall ($N = 1{,}138$)	Breast-conserving therapy ($n = 366$)	Mastectomy only ($n = 354$)	Mastectomy and radiotherapy ($n = 418$)	*p* Values	Adjusted odds ratio for postmastectomy radiotherapy[1]
First generation	63 (8.7)	35 (14.5)	20 (11.6)	8 (2.6)		1.10 (0.34–3.54)
Second generation	540 (74.6)	177 (73.4)	135 (78.5)	228 (73.3)		3.64 (2.18–6.09)[2]
Third generation	121 (16.7)	29 (12.0)	17 (9.9)	75 (24.1)		9.75 (4.41–21.5)[2]
Unknown regime	137	35	48	54		

[1]Only included 772 patients subjected to mastectomy. Derived using logistic regression adjusted for center, age at diagnosis, ethnicity, tumor size, number of positive lymph nodes, tumor grade, lymphovascular invasion, neoadjuvant chemotherapy administration, surgical margin status and chemotherapy details.
[2]Statistically significant.
[3]Entered as a continuous variable in the logistic regression model.

involvement),[22–24] we stratified our patients into those with T1-2, N0-1 tumors and T3-4, N2-3 tumors.[4,5,8] Relative survival of TNBC patients was compared between those treated with BCT, mastectomy only and postmastectomy radiotherapy. To adjust for baseline differences in demographic, tumor and treatment characteristics between the three groups, we used Cox regression analysis to estimate the hazard ratios (HRs). Prognostic factors that were included in the multivariable Cox model were selected based on *a priori* knowledge of their associations with breast cancer survival, age at diagnosis, ethnicity, tumor size, number of pathologically positive axillary lymph nodes, tumor grade, lymphovascular invasion, surgical margin status, neoadjuvant chemotherapy, adjuvant chemotherapy and type of chemotherapy. We also adjusted the model for "center of treatment" to account for differences in patients characteristics and treatment choices between the different centers.

As chemotherapy is the main mode of treatment in TNBC, interaction between locoregional treatment and type of adjuvant chemotherapy was tested by including an interaction term for chemotherapy [no, yes (first generation), yes (second generation), yes (third generation)] and locoregional treatment into the multivariable model. We also tested whether the impact of chest wall radiotherapy on overall survival differed between older and younger women[25] using an interaction term for age (<40, 40–64, ≥65) and locoregional treatment. Given the relatively small number of patients in some age strata, multivariable Cox models were fitted using a stepwise backward regression approach.

Missing values (ranging between 5 and 30%) were imputed by multiple imputation, where all variables of the multivariable regression model were included in the imputation model and ten imputation sets were created.

Results

Women of Chinese ethnicity comprised 72% of the cohort, followed by women of Malay (13%), Indian (9%) and other ethnicities (6%). Median age at diagnosis was 53 years and ranged from 23 to 96 years. Median tumor size at diagnosis was 2.5 cm and close to 60% of patients had lymph node-negative disease. Most patients presented with Stage II disease (45%), followed by Stage I (28%) and Stage III (27%) breast cancer. Approximately 80% of patients had poorly differentiated tumors and lymphovascular invasion was present in 34% of patients.

Overall, 144 TNBC patients (13%) received neoadjuvant chemotherapy. These women largely comprised those with T3-4, N2-3 tumors (∼70%). The majority of TNBC patients in our study received adjuvant chemotherapy ($n = 861$, 76%) comprising predominantly anthracycline-based regimes (Table 1). Taxanes were more likely to be administered in patients with bigger tumors and/or higher lymph node involvement ($p < 0.001$). Adjuvant chemotherapy was administered in 74% of patients with T1-2, N0-1 (early) tumors, out of which taxane-based regimes were given to 15%. Among women with T3-4, N2-3 (locally advanced) tumors, 82% had received adjuvant chemotherapy, and approximately 25% of these women received taxane-based chemotherapy (not shown).

Patients who underwent BCT were substantially younger (median age = 49 years) than those receiving mastectomy only (59 years) or mastectomy with radiotherapy (53 years) (Table 1). Mastectomy was administered in 42% of patients with Stage I disease and in 73% of those with Stage II breast cancer. Axillary lymph nodes were negative in 528 (∼75%) patients who underwent BCT or mastectomy only, whereas close to 70% of patients receiving postmastectomy radiotherapy had lymph node involvement. Patients with high-grade tumors and lymphovascular invasion more often received adjuvant radiotherapy, regardless of type of surgery. Patients subjected to postmastectomy radiotherapy more frequently received neoadjuvant chemotherapy, had positive surgical margins and received taxane-based chemotherapy (Table 1). In a multivariable logistic regression analysis, postmastectomy radiotherapy was significantly and independently associated with younger age at diagnosis, larger tumors, increasing

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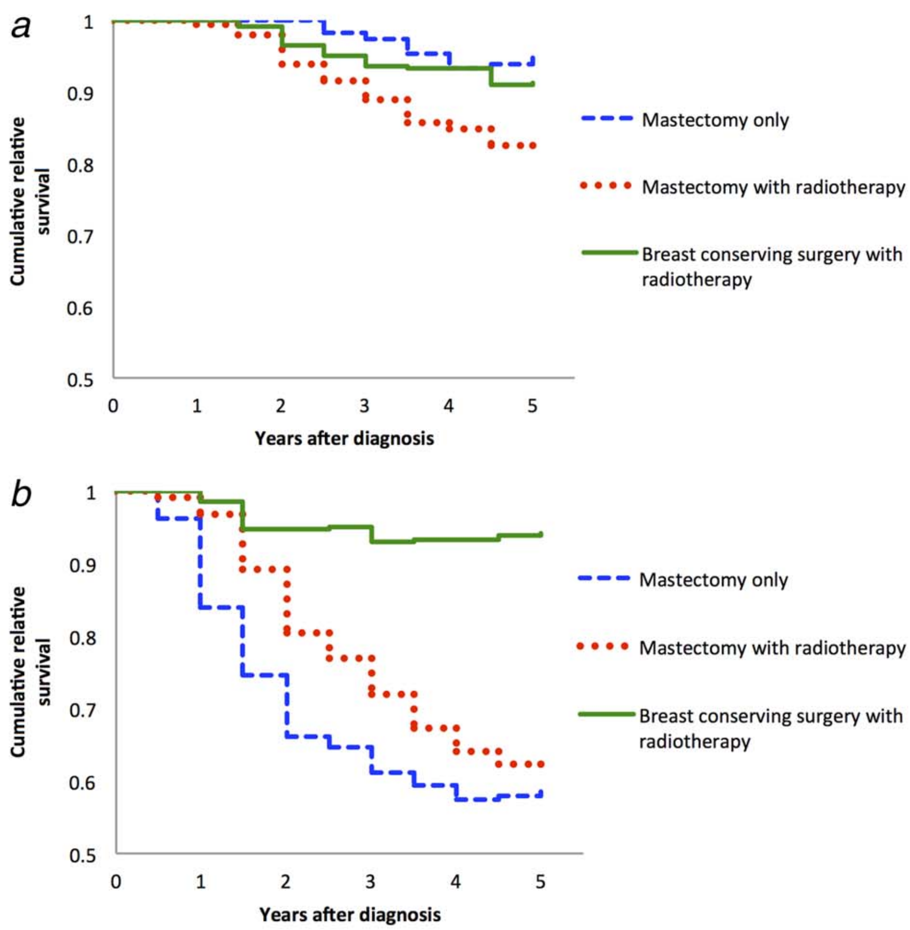

Figure 1. (a) Relative survival after diagnosis with triple-negative breast cancer by type of locoregional management in 775 Asian women with T1-2, N0-1 tumors. (*b*) Relative survival after diagnosis with triple-negative breast cancer by type of locoregional management in 363 Asian women with T3-4, N2-3 tumors. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

axillary nodal burden, neoadjuvant chemotherapy, positive surgical margins and second- or third-generation adjuvant chemotherapy administration.

Among the 775 TNBC patients with T1-2, N0-1 tumors, 75 women died during 2,780 person-years of follow-up. The corresponding 5-year relative survival ratio (RSR) was 90.1% (95% CI: 86.5–93.0%). The survival of women treated with mastectomy only was not significantly different compared to patients receiving BCT (5-year RSR: 94.7%, 95% CI: 88.8–98.8% *versus* RSR: 90.8%, 95% CI: 85.0–94.7%) (Fig. 1a). Women treated with mastectomy with radiotherapy, however, had significantly lower survival than women undergoing mastectomy alone (5-year RSR: 82.3%, 95% CI: 73.4–88.1%) (Table 2). The association between locoregional treatment and overall survival was not modified by type of adjuvant chemotherapy; p for interaction with adjuvant chemotherapy details $= 0.151$. Following full adjustment for demographic, tumor and treatment characteristics, patients treated with BCT had a similar mortality risk as women who underwent mastectomy only (HR: 0.84, 95% CI: 0.43–1.65), as did women treated with mastectomy and radiotherapy (HR 1.07, 95% CI: 0.56–2.04).

Of the 363 patients with T3-4, N2-3 TNBCs, 109 women died during 1,166 person-years of follow-up. In these women, the 5-year RSR was 67.2% (95% CI: 60.8–72.9%). Patients subjected to BCT had the highest survival (5-year RSR: 94.1%, 95% CI: 81.3–99.4%) (Table 2). Among patients receiving mastectomy, those treated with postmastectomy radiotherapy experienced higher survival than those without: 5-year RSR 62.7% (95% CI: 54.3–70.1%) *versus* 58.6% (95% CI: 43.5–71.6%), respectively (Fig. 1b). There was significant interaction between locoregional treatment and type of adjuvant chemotherapy (p for interaction test $= 0.010$) in women with T3-4, N2-3 TNBCs. Following multivariable adjustment, patients subjected to postmastectomy radiotherapy had significantly lower risk of death than patients with mastectomy alone; HR: 0.48 (95% CI: 0.27–0.85). The adjusted HR for mortality in patients subjected to BCT was 0.20 (95% CI: 0.06–0.60) compared to those with mastectomy alone.

Age significantly modified the impact of locoregional treatment on breast cancer survival (p for interaction test $= 0.006$). Age-stratified analysis showed a 5-year RSR of 71.7% (95% CI: 61.4–79.8%) in very young women ($<$40

Table 2. Association between locoregional treatment and survival in 1,138 Asian women with nonmetastatic triple-negative breast cancer

	No. of patients	No. of deaths	5-Year relative survival[1] (95% CI)	Crude hazard ratio (95% CI)	Adjusted hazard ratio[2] (95% CI)
T1-2, N0-1 tumors	775	75	90.1% (86.5–93.0%)	–	–
Breast-conserving therapy	311	23	90.8% (85.0–94.7%)	0.82 (0.47–1.43)	0.84 (0.43–1.65)
Mastectomy only	286	25	94.7% (88.8–98.8%)	1.00	1.00
Mastectomy and radiotherapy	178	27	82.3% (73.4–88.1%)	1.77 (1.05–2.99)[3]	1.07 (0.56–2.04)
T3-4, N2-3 tumors	363	109	67.2% (60.8–72.9%)	–	–
Breast-conserving therapy	55	4	94.1% (81.3–99.4%)	0.15 (0.05–0.42)[3]	0.20 (0.06–0.60)[3]
Mastectomy only	68	29	58.6% (43.5–71.6%)	1.00	1.00
Mastectomy and radiotherapy	240	76	62.7% (54.3–70.1%)	0.43 (0.27–0.68)[3]	0.48 (0.27–0.85)[3]

[1]Derived using the Ederer II method; ratio of observed survival in women with breast cancer to the survival that would have been expected for the women of the general population, which is matched for age, calendar time and country of residence. Expected survival was derived from the respective life tables for the Malaysian, Singaporean and Hong Kong populations.
[2]Derived using Cox regression adjusted for center (UMMC, NUH, NCCS, TTSH, QMTWH), age at diagnosis, race, tumor size at diagnosis, number of positive axillary lymph nodes, tumor grade (low, moderate, high), surgical margins (free, involved), lymphovascular invasion (present, absent), neoadjuvant chemotherapy (yes, no) and adjuvant chemotherapy administration and regime (none, first generation, second generation, third generation).
[3]Statistically significant.

Table 3. Association between locoregional treatment and survival of Asian women with nonmetastatic triple-negative breast cancer by age group

	No. of patients	No. of deaths	Crude hazard ratio (95% CI)	Adjusted hazard ratio[1] (95% CI)
Very young women < 40 years	148	31	–	–
Breast-conserving therapy	78	4	0.08 (0.03–0.26)[2]	0.10 (0.03–0.34)[2]
Mastectomy only	23	12	1.00	1.00
Mastectomy and radiotherapy	47	15	0.53 (0.25–1.13)	0.20 (0.08–0.50)[2]
Middle-aged women 40–64 years	785	109	–	–
Breast-conserving therapy	243	18	0.66 (0.36–1.23)	0.70 (0.37–1.32)
Mastectomy only	190	23	1.00	1.00
Mastectomy and radiotherapy	243	68	2.22 (1.39–3.57)[2]	1.06 (0.63–1.78)
Elderly women ≥ 65 years	205	44	–	–
Breast-conserving therapy	22	5	1.09 (0.41–2.91)	1.51 (0.51–4.45)
Mastectomy only	99	19	1.00	1.00
Mastectomy and radiotherapy	40	20	2.14 (1.14–4.02)[2]	1.34 (0.67–2.68)

[1]In very young women, HR was derived using a stepwise backward Cox regression model. Variables entered on step 1 are center, age at diagnosis, race, tumor size at diagnosis, number of positive axillary lymph nodes, tumor grade (low grade, moderate high grade), surgical margins (free, involved), lymphovascular invasion (present, absent) and chemotherapy administration and regime (none, first generation, second generation, third generation). Final model includes age at diagnosis, tumor size at diagnosis, number of positive axillary lymph nodes, lymphovascular invasion (present, absent) and neoadjuvant chemotherapy administration (yes, no). In women aged 40–64 years old, HR was derived using similar method as in very young women. Final model includes center, age at diagnosis, tumor size at diagnosis, number of positive axillary lymph nodes, tumor grade (low grade, moderate high grade), lymphovascular invasion (present, absent) and neoadjuvant chemotherapy administration (yes, no). In women aged ≥65 years, HR was derived using similar method as in very young women. Final model includes center, tumor size at diagnosis, number of positive axillary lymph nodes and lymphovascular invasion (present, absent).
[2]Statistically significant.

years), 84.9% (95% CI: 81.4–87.8%) in women aged 40–64 years and 81.6% (95% CI: 71.0–90.2%) in the elderly (≥65 years). In 148 very young women, both BCT and mastectomy with radiotherapy were significantly associated with a higher survival compared to mastectomy only [adjusted HR: 0.10 (95% CI: 0.03–0.34) and 0.20 (95% CI: 0.08–0.50), respectively]. However, in the older age groups, neither BCT nor postmastectomy radiotherapy was associated with a survival advantage (Table 3).

We additionally performed a subgroup analysis dividing women into two broader age groups; age <50 years and ≥50 years. In 258 women aged <50 years with negative lymph nodes, both BCT and mastectomy with radiotherapy were not associated with a survival advantage compared to mastectomy alone; adjusted HR: 0.44 (95% CI: 0.09–2.22) and 0.89 (95% CI: 0.27–2.90), respectively. In 283 women aged ≥50 years with lymph node involvement, the corresponding adjusted HRs were 0.64 (95% CI: 0.19–2.22) and 0.88 (95% CI: 0.45–1.73).

To enable comparisons with studies of Abdulkarim *et al.*[4] and Zumsteg *et al.*,[8] we also performed a subgroup analysis of 577 TNBC patients with T1-2, N0 tumors. In this subgroup, adjuvant radiotherapy was not significantly associated with improved survival; HR for BCT *versus* mastectomy alone was 1.22 (95% CI: 0.56–2.63), whereas HR for mastectomy with radiotherapy compared with mastectomy alone was 2.00 (95% CI: 0.88–4.55) (Table 2).

Sensitivity analyses employing missing data indicator method[26] to address missing variables did not change the inferences. Stratified analyses by center of treatment, instead of multivariable adjustment by treatment center, did not modify the point estimates.

Discussion

Findings from this multiethnic cohort of South-East Asian patients with TNBC suggest that adjuvant radiotherapy following breast-conserving surgery or mastectomy is associated with a survival advantage in patients with locally advanced tumors and in very young women (aged < 40 years).

The value of adjuvant radiotherapy for TNBC has been recently the object of several controversial reports. Retrospective analysis of breast cancer patients from the Danish Breast Cancer Cooperative Group (DBCG) 82b and 82c trials whom had either positive lymph nodes and/or T3-4 tumor showed no survival benefit for postmastectomy radiation within those with triple negative disease.[27] However, only 152 patients in the above study had TNBC, limiting the power of the analysis. On the other hand, a prospective randomized controlled multicenter trial in China, including a similar cohort as in our study in terms of young age and large tumors, demonstrated that postmastectomy radiation therapy was associated with significant improvements in recurrence-free and overall survival compared to mastectomy alone in women with Stage I and Stage II TNBC.[5] A concern in this trial was that it was commenced before TNBC became the focus of attention and lack information on data quality assurance. A large observational registry-based study in a single Canadian province showed that compared to mastectomy alone, BCT was associated with improved recurrence-free survival in patients with T1-2, N0 TNBC, but not with a significant overall survival advantage.[4] This finding was however not confirmed in other studies.[6–9] Most of the previous studies included a wide spectrum of patients with varying disease stages.[6,7,9,27] Hence, candidates selected to receive adjuvant radiotherapy were substantially different in terms of prognosis from those receiving surgery only, making it difficult to assess the "genuine treatment effect." In an attempt to reduce the baseline prognostic differences in the study population, a very recent observational study only included patients with T1-2, N0 TNBC.[8] In this study, BCT was not significantly associated with a survival advantage compared to mastectomy alone in very early TNBC. Another study, which also stratified patients based on risk of locoregional recurrence, showed that in women with T3-4, N2-3 TNBC, administration of postmastectomy radiotherapy significantly improved locoregional recurrence-free survival and disease-free survival during a median follow-up of 65 months.[28] Given that overall survival was not studied as an endpoint in the above study, it is felt that our study finding compliments the above results, where we have shown that postmastectomy radiotherapy is also associated with an overall survival gain in patients with T3-4, N2-3 TNBC.

The finding that adjuvant radiotherapy may provide substantial survival benefit in very young women with TNBC had never been reported. Although this subgroup was small and hence may have produced imprecise point estimates, the age effect, which is important in Asian cohorts, may partly explain the difference in findings between various studies. The mechanism by which adjuvant radiotherapy may exert its protection in very young women with TNBC is unknown. A plausible hypothesis would be that presence of an underlying BRCA gene mutation in these women might have influenced their response to adjuvant radiotherapy.[29] This is based on several experimental and clinical studies, which appears to suggest that tumors harboring BRCA1/BRCA2 mutation are more sensitive to ionizing radiation[30–32] and alkylating chemotherapy regimes.[33]

To date, this is the largest cohort study, which exclusively studied multiethnic Asian women with triple negative disease. While we did not have data on cause of death for a majority of our patients to allow estimation of breast cancer-specific survival, we computed relative survival. Relative survival provides an estimate of net survival attributed to TNBC given that it captures both the direct and indirect contribution of cancer diagnosis on survival.[21] Furthermore, it also takes into account systematic differences in the background mortality risk between the populations in Malaysia, Singapore and Hong Kong. Nevertheless, breast cancer is more common in women with higher levels of education and income,[34] making life expectancies between the patients and the background population not entirely comparable. It hence remains possible that (relative) survival may have been slightly overestimated in our study due to mismatch in the socioeconomic status between the breast cancer patients and the background population of Malaysia, Singapore and Hong Kong. It is acknowledged that selection bias may pose a problem in our study given its observational nature. Patients subjected to postmastectomy radiotherapy were a selected subgroup based on indication, *i.e.*, encompassing those with poor prognostic features such as large tumors and high nodal burden. Although we adjusted for multiple confounders, we were unable to account for unmeasured confounders such as cardiovascular comorbidities and BRCA mutation status. While it is acknowledged that we may have included a number of women with very weak ER expression (1–9%) in our study, the very low proportion of these women[35] is unlikely to have impacted our inferences.

Conclusions

Based on this observational study, it appears that in women with T1-2, N0-1 TBNC, adjuvant radiotherapy is not associated with survival following breast cancer. However, adjuvant radiotherapy appears to be associated with improved survival in women with T3-4, N2-3 tumors, independent of the type of surgical procedure and chemotherapy. Age appears to modify the association between adjuvant radiotherapy and survival in TNBC. Our research findings warrant confirmation in clinical trials. Such trials should include women of different ethnicities and settings to enable appropriate translation in clinical practice worldwide.

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